Lymphomas of Large Cells

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SUMMARY

Historical aspects of the classification of large-cell lymphomas are described. Immunological characterization of the lymphomas has been made possible by identification of T and B lymphocytes according to their cell membrane surface characteristics. The pathogenesis of lymphomas has been clarified by the germinal (follicular) centre cell concepts of Lennert and Lukes and Collins. The various classifications are presented and compared. Whether these subdivisions will have any relevance in the clinical context remains to be seen.

S. Afr. med. J., **52**, 438 (1977).

In 1948 Willis[1] wrote: 'Nowhere in pathology has a chaos of names so clouded clear concept as in the subject of lymphoid tumours.' Unfortunately this position has not changed, as evidenced by the plethora of classifications (see Table I) presented in the last 3 years. Architecturally, lymphomas may be diffuse or follicular. Since 1964 Lennert *et al.*,[2,3] on the basis of their electron microscopical studies, have steadfastly maintained that follicular lymphoma was a distinct pathological entity and this has now received widespread acknowledgement.[4,5-7] No matter what terminology is used, there also seems to be general acceptance of two types of small-cell lymphoma, one with normal-appearing lymphocytes and one with pleomorphic cleaved lymphocytes, termed well-differentiated lymphocytic lymphoma and poorly differentiated lymphocytic lymphoma respectively.[8] All classifications also include a lymphoma consisting of small lymphocytes with plasmacytoid features. The area of greatest controversy concerns the lymphomas of large cells.

HISTORICAL ASPECTS

Before 1930 malignant lymphomas were divided into Hodgkin's disease and lymphosarcoma, the latter including many morphological variants. In 1930 Roulet[9,10] used the term 'Retothelsarkom' for large-cell lymphomas, which he thought were derived from reticulum cells not classifiable as lymphoid. Thus the term reticulum cell sarcoma was applied to all large-cell lymphomas.

In 1942 Gall and Mallory[11] abandoned the term reticulum cell sarcoma in favour of two terms which they considered more specific. Stem-cell lymphoma, was used for highly undifferentiated cells, and clasmatocytic lymphoma for well-differentiated cells with phagocytic properties. They introduced the term lymphoblastic lymphoma for the immature lymphoid malignancies.

In 1958 Gall and Rappaport[12] changed the terminology of the previous classification by substituting the term histiocytic lymphoma for clasmatocytic lymphoma. A new entity, the histiocytic-lymphocytic (mixed cell) type, was introduced for lymphomas with a mixture of small and large cells. The term lymphoblastic lymphoma was now changed to lymphocytic type, poorly differentiated. Rappaport's[8] subsequent classification in 1966 differed in only two respects from the earlier one.[12] Stem-cell lymphoma was replaced by malignant lymphoma, undifferentiated, and virtually all other large-cell lymphomas were lumped together as malignant lymphoma, histiocytic. Lukes' classification in 1968[13] omitted mixed histiocytic-lymphocytic lymphoma because he maintained that it represented a variation in a single cell, the histiocyte.

Meanwhile, from 1964 to 1966, Lennert *et al.*,[2,3] as a result of studies of germinal centres, described three types of cells: germinocytes, germinoblasts and reticulum cells. They postulated that follicular lymphomas were derived from neoplastic proliferations of these three cell lines. This was the forerunner of the follicular centre cell concept of Lukes and Collins.[4,14]

Burkitt's tumour, the malignant lymphoma first described in Black African children, was first morphologically characterized by O'Connor[15] in 1961. A WHO Bulletin[16] issued in 1969 stated that Burkitt's type lymphoma should be recognized as a separate entity on clinical and morphological criteria. This has been generally accepted.

T and B Lymphocytes

In the 1950s and 1960s, surgical extirpation of lymphoid organs in animals was used to define the various lymphoid populations, and the concept of T and B lymphocytes arose.[17-21] The T cell, or thymus-dependent cell, was associated with cellular immunity, and the B cell, or bursa-equivalent cell, with humoral immunity. Similar systems exist in man.[22] B lymphocytes are present in the germinal centres and medullary cords of lymph nodes, while T lymphocytes are in the paracortical areas. In 1960 Nowell[23] described the mitogenic effect of phytohaemagglutinin (PHA) on blood lymphocytes. This transformation involved the induction and enhancement of RNA and protein synthesis and the initiation of cell division. Activated cells transform into blast-like cells before or during DNA synthesis. These transformed lymphocytes, when stained with Giemsa, resemble blast cells with deeply basophilic cytoplasm, and are at least four times the size of a small lymphocyte.

Different stages in the transformation phenomenon are responsible for varying morphological features of lympho-

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Date received: 9 February 1977.

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TABLE I. COMPARISON OF CLASSIFICATIONS OF LARGE-CELL LYMPHOMAS

Old popular terminology	Rappaport (1966)	Dorfman (1974)	Bennett *et al.* (1974)	Kiel (1974)	Lukes and Collins (1974)	WHO (1976)
Lymphosarcoma	Lymphocytic, poorly differentiated	Atypical small lymphocytic	Lymphocytic, poorly differentiated	Lymphoblastic		Lymphosarcoma, diffuse
		Convoluted lymphocytic		Convoluted cell type	Convoluted lymphocytic	Lymphoblastic convoluted nuclei
	Mixed lymphocytic-histiocytic	Mixed small and large lymphoid	Mixed small lymphoid and undifferentiated large cell	Centrocytic-centroblastic	—	Lymphosarcoma, prolymphocytic and lymphoblastic
	Histiocytic, well differentiated	Histiocytic	True histiocytic	Histiocytic	Histiocytic	—
Reticulum cell sarcoma	Histiocytic, poorly differentiated	Large lymphoid pyroninophilic	Undifferentiated large cell	Centroblastic, immunoblastic	Large non-cleaved immunoblastic sarcoma	Lymphosarcoma, immunoblastic
	—	—	Lymphocytic, poorly differentiated lymphoblastic	Lymphoblastic	Small non-cleaved	Lymphoblastic
	Undifferentiated, pleomorphic	Undefined, undifferentiated	—	—	Large cleaved cell	Reticulo-sarcoma

cytes, which were previously interpreted as different degrees of lymphocyte differentiation. In histological sections these cells have a primitive neoplastic appearance and undergo many mitoses, and their cytoplasm stains intensely with methyl green pyronin (pyroninophilia). As a result of the observations of Lukes *et al.*[24,25] these cells became known as immunoblasts. They were recognized as normal constituents of the interfollicular and intrafollicular tissues of antigenically stimulated nodes, increasing in regional nodes after smallpox vaccination or in infectious mononucleosis.

In 1968 Good and Finstad[22] documented the association of lymphoid malignancy with immunological malfunction. Since then receptors and antigens have been identified on immunologically competent cells, which provide information as to their origin (Table II). In 1970 Raff[26] demonstrated that B lymphocytes had immunoglobulin on their surface. In the same year, most B lymphocytes were shown to have a receptor for antigen-antibody complement complexes, which was detected by using red cells (E) coated with antibody (A) and complement (C).[27] In man, Lay *et al.*[28] demonstrated rosette formation with T lymphocytes and sheep red blood cells. Monocytes and macrophages also bear a receptor for EAC,[29] and a receptor for antigen-antibody complexes which is detectable by use of red cells coated with immunoglobulin G (EA).[30] These membrane surface markers allow the positive identification of T and B lymphocytes, monocytes and macrophages. In 1973, Shevach *et al.*[31] used these membrane surface markers in the identification of the origin of the cells in lymphoproliferative malignancies.

TABLE II. MEMBRANE SURFACE MARKERS

Cell	IgM - EAC	IgG-EA
B lymphocyte	+	−
T lymphocyte	−	−
Monocyte	+	+
Macrophage	+	+

Follicular Centre Cell Concept

Starting in 1971, Lukes and Collins,[4,32] on the basis of their studies of morphology, proposed the follicular centre cell concept. They considered the cells of the follicular centre to be components of the B cell system and to consist of four types of cells: (*i*) cleaved nucleated cells; (*ii*) non-cleaved nucleated cells; (*iii*) tingible body macrophages or 'starry-sky' phagocytes; and (*iv*) dendritic reticular cells. The predominant cells are the cleaved and non-cleaved cells whose frequency varies with the state of activity of the follicle. These cells vary in size and in the stage of nuclear cleavage. Pyroninophilia, scanty in the cleaved cells, increases in the non-cleaved cells as the nucleus increases in size. Lukes and Collins considered the follicle

to be the site of normal lymphocyte transformation, proceeding from small cleaved, large cleaved, small non-cleaved to large non-cleaved cells. Only the non-cleaved cells possess nucleoli and are the dividing cells of the follicular centre. Thus transformation proceeds from the small dormant lymphocyte to the large, metabolically active dividing form. From their morphological studies of the malignant lymphomas of follicular centre cells, Lukes and Collins suggested evidence of blocks in transformation of 'switch on' (derepression) from the cleaved to the non-cleaved cells. The lymphomas of follicular centre cells were divided into four categories: (*i*) small cleaved; (*ii*) large cleaved; (*iii*) small non-cleaved; and (*iv*) large non-cleaved. Later this concept was expanded by means of immunological studies and the lymphomas were divided into T and B cell types.[14,33] On the basis of their classification the large-cell lymphomas were mainly of B cell origin, i.e. large cleaved and large non-cleaved follicular centre types. Immunoblastic sarcoma could be of both B and T cell origin.

Lennert's Germinal Centre Concept

During the same period (1971 - 1974) Lennert[34-36] expanded on his concept of cells arising from the germinal centre; this idea had many similarities to the follicular centre cell concept. The large cells in the germinal centre were named germinoblasts. In 1974 he put out a new classification, in which he divided lymphomas into those of low-grade and those of high-grade malignancy.[37] The lymphomas of high-grade malignancy consisted of large cells and were subdivided into germinoblastoma, lymphoblastoma and immunoblastoma. In 1974 Lennert[38] issued the Kiel classification, in which the term germinoblastoma was changed to centroblastoma. In using the term centroblastoma, Lennert has further subdivided the transformed lymphocyte group. The centroblast in many respects resembles the immunoblast, but it is slightly smaller. Both cells have basophilic cytoplasm with large nuclei. The centroblast has nucleoli along the nuclear membrane while the immunoblast has a much larger central nucleolus. The centroblast is the precursor of the immunoblast during lymphocyte transformation.[39] This tumour represents the anaplastic end phase of follicular lymphoma.[38] It is the equivalent of Lukes and Collins' large non-cleaved lymphoma.

Lennert states that he has often seen a combination of centrocytes, centroblasts and immunoblasts in lymphoid tumours. Since the majority of the cells in these tumours are centroblasts, he classifies them as centroblastic lymphomas. The centrocytes indicate that they are germinal centre tumours. The immunoblasts present in the tumour may develop from the centroblasts. Lennert used to include this group of tumours in the group of immunoblastic lymphomas because he believed that the immunoblast was the cell with the highest degree of differentiation. However, he has now removed these tumours from the immunoblastic group, since they differ from the other immunoblastic lymphomas in that their tumour cells form EAC rosettes.[39]

Classification of Bennett *et al.*

In June 1973, at a workshop on the classification of non-Hodgkin's lymphoma, Bennett *et al.*[5] presented their classification. Their lymphocytic, poorly differentiated group incorporated the lymphoblastic lymphomas, which corresponded to the similarly designated group in Lennert's classification. The undifferentiated large-cell group consisted of large lymphoid cells, i.e. transformed lymphocytes with strongly basophilic (pyroninophilic) cytoplasm.

Dorfman's Classification

In 1974, Dorfman[6] proposed a classification that did not differ fundamentally from that of Rappaport.[8] However, he included the lymphoblastic group with the atypical small lymphocytic group, and the large-cell lymphomas were known as large lymphoid (pyroninophilic) lymphomas.

WHO Classification

In 1976 Mathé *et al.*[7] issued the WHO classification of haematological malignancies. Using cytological and histological criteria, they divided the large-cell lymphomas into lymphoblastic and immunoblastic lymphomas and reticulosarcomas. The latter term is used for malignant tumours which show evidence of production of argyrophilic fibres or phagocytosis, or both, and in which there are conspicuous variations in cellular and nuclear shapes.

UNIFICATION

Of the above six classifications, those of Dorfman,[4] Bennett,[5] Lennert[38] and Lukes and Collins[14] recognize histiocytic lymphoma as a very rare entity, with positive alpha-naphthyl-acetate esterase staining[33,40] on lymph node imprints. Rappaport's classification[8] included many morphological variants under the term histiocytic. In the WHO classification,[7] histiocytic lymphoma is not mentioned. It is now realized that most cases termed 'histiocytic' lymphoma are in reality transformed lymphocytes or immunoblasts. This type of large-cell lymphoma has been called histiocytic (Rappaport), large lymphoid (Dorfman), undifferentiated large cell (Bennett), centroblastic, immunoblastic (Lennert) immunoblastic sarcoma (Lukes and Collins) and immunoblastic (WHO).

The term lymphoblastic lymphoma, as proposed by Gall and Mallory,[11] has now been reintroduced and is used by Bennett, Lennert and the WHO classification. Dorfman includes it under atypical small lymphocytic tumours, Rappaport as poorly differentiated lymphocytic lymphoma, and Lukes and Collins as small non-cleaved cell tumour. It is interesting to note that recently Nathwani *et al.*[41] have used the term malignant lymphoma, lymphoblastic, as a variant of poorly differentiated lymphocytic lymphoma to describe convoluted and non-convoluted forms in children and adolescents, and sometimes associated with acute lymphoblastic leukaemia.

All the classifications except that of Lennert allow for an unclassifiable or undefined group, to which Rappaport simply refers as undifferentiated, pleomorphic. The Lukes

and Collins classification describes the large cleaved cell as an entity. It is difficult to fit this cell, as described, into the other classifications. Presumably it would fit into the unclassified undefined or undifferentiated types. The WHO classification would probably include it in the reticulosarcoma group, providing it produced reticulin or exhibited phagocytosis. Many of these irregular or large cleaved cells may result from technical inadequacies in fixation and processing,[6] as their imprints show normal rounded cells. It must be pointed out that imprints obtained with the convoluted type of lymphoblastic lymphoma[41] exhibit convolutions of the nuclei of the lymphoblastic cells. In Lennert's classification there is no group which corresponds with the large cleaved cell of Lukes and Collins; he believes that these cells may be unclassified lymphoblastic lymphomas which often have cleaved nuclei.[39]

Braylan *et al.*[42] have divided the large-cell lymphomas into three major categories:

1. Monomorphic cells with round to oval vesicular nuclei, one to three eosinophilic nucleoli, and pyroninophilic cytoplasm. These cells most closely resemble immunoblasts or transformed lymphocytes.

2. Uniform cells with indented or lobulated nuclei and usually single and moderately prominent nucleoli. The cytoplasm is relatively abundant and only faintly pyroninophilic. This description is most like that of the large cleaved cell of Lukes and Collins.[33]

3. A very pleomorphic and bizarre group which includes multinucleate giant cells. Foci of necrosis, interstitial fibrosis and inflammatory elements suggest Hodgkin's disease.

Most classifications include three basic cell types comprising the common large-cell lymphomas:

Immunoblastic, a term used by Lennert, Lukes and Collins, and Mathé (WHO), which was labelled as histiocytic by Rappaport, as large lymphoid by Dorfman and as undifferentiated large cell by Bennett *et al.* This cell is a transformed lymphocyte and is a large cell with a moderate amount of strongly basophilic (pyroninophilic) cytoplasm. It has a large nucleus, usually with a single prominent nucleolus (Fig. 1). The centroblast is a cell type described only by Lennert. It is a medium-sized to large cell with scanty basophilic cytoplasm and it has two to three meduim-sized nucleoli situated at the nuclear membrane (Fig. 2).

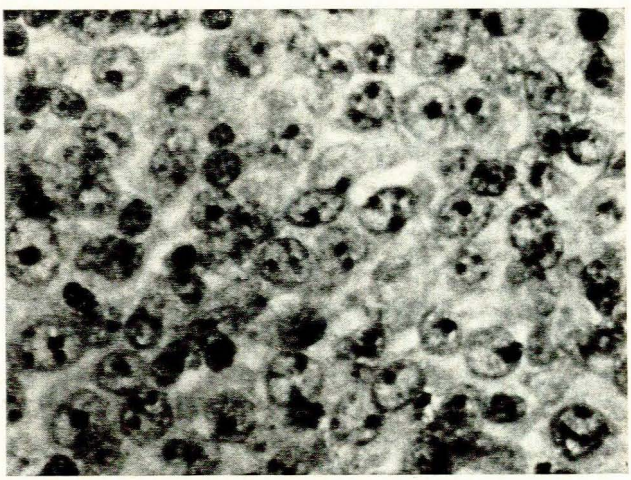

Fig. 1. Immunoblasts — these cells are transformed lymphocytes and may be of T or B cell origin. They are large cells with a moderate amount of strongly basophilic (pyroninophilic) cytoplasm. Their vesicular nuclei are round to oval usually with one prominent nucleolus. (H and E × 500.)

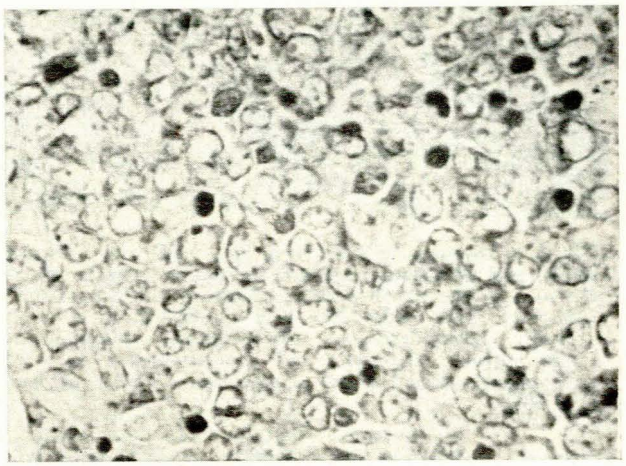

Fig. 2. Centroblasts — Lennert describes this cell as a distinctive cell type and regards it as the precursor cell of the immunoblast. It is a medium-to-large cell with scanty basophilic cytoplasm, a large nucleus and two to three small nucleoli situated at the nuclear membrane. (H and E × 400.)

Taylor[43] has used immunoperoxidase techniques for the demonstration of intracellular immunoglobulins in certain large-cell lymphomas, thereby confirming their B cell origin. Like Lennert[34-36] and Lukes and Collins,[4] he relates the various histological types of lymphoreticular neoplasms to morphological forms of the lymphocyte which are assumed during transformation. The fact that one may see several cell types in a lymphomatous neoplasm is well known, hence the terms polymorphic reticulosarcoma[44,45] and polymorphic immunocytoma[39] (Fig. 3).

Recently Fisher *et al.*[46] described a case of immunoblastic lymphadenopathy which evolved into a malignant lymphoma with plasmacytoid features. This malignancy fitted in well with the description applied to immunoblastic sarcoma as described by Lukes and Collins.[14] Mathe *et al.*[47] have described an immunoblastic lymphoma which quickly evolved into a leukaemic phase. In the description of Lukes and Collins[14] these cells may occasionally include prominent abnormal plasma cells. Electron microscopy of the tumour in Fisher's case revealed a prominent rough endoplasmic reticulum lined with ribosomal particles.[46] The tumour in Mathé's case[47] showed a paucity of rough endoplasmic reticulum. Therefore Fisher's case was of plasmacytic origin and Mathé's of lymphocytic origin. It seems that the term immunoblastic sarcoma has been applied to a heterogeneous group.

Lymphoblastic, a term used by all except Rappaport, who includes it under poorly differentiated lymphocytic

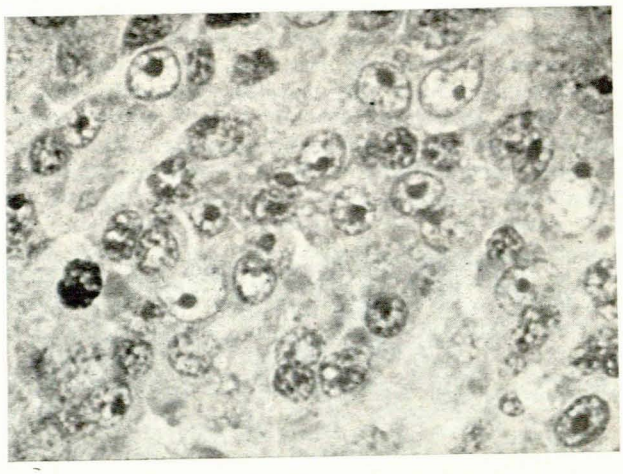

Fig. 3. A spectrum of cells, from large cells with vesicular nuclei and prominent nucleoli to smaller cells in which the nuclear chromatin becomes clumped and the nucleoli indistinct. This entity has been described as a polymorphic reticulosarcoma (Robb-Smith), polymorphic immunocytoma (Lennert) and immunoblastic sarcoma with plasmacytoid features (Lukes and Collins). (H and E × 500.)

lymphoma, Dorfman, who classifies it with his atypical small lymphocytic group, and Lukes and Collins, who call it small non-cleaved lymphoma. These are medium-sized cells with scanty basophilic cytoplasm which resemble the lymphoblasts of acute lymphoblastic leukaemia. They have large nuclei with fine chromatin and with small or medium-sized nucleoli (Fig. 4). Among these cells are often found macrophages exhibiting phagocytosis, giving the characteristic 'starry sky' appearance.

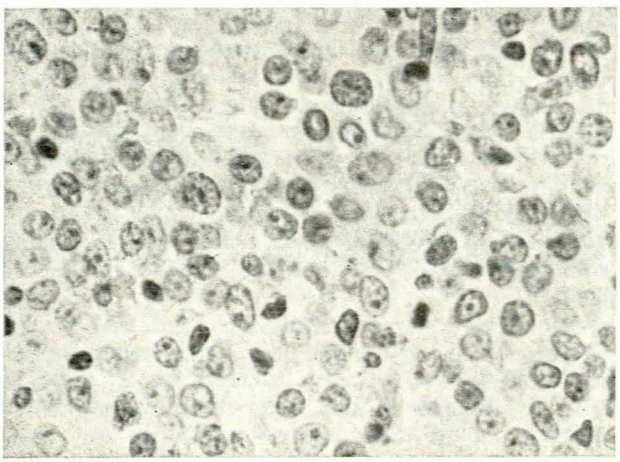

Fig. 4. Lymphoblasts — these medium-sized cells have scanty basophilic cytoplasm. The nuclei are fairly large with fine chromatin and with small or medium-sized nucleoli. (H and E × 400.)

Large cleaved cell. This term is used only by Lukes and Collins. Mathé would include it in the reticulosarcoma group, providing it formed reticulin or exhibited phagocytosis. These are large cells with a narrow rim of basophilic (pyroninophilic) cytoplasm, and a large cleaved nucleus with an inconspicuous nucleolus (Fig. 5). They may sometimes appear rounded on imprint preparations.

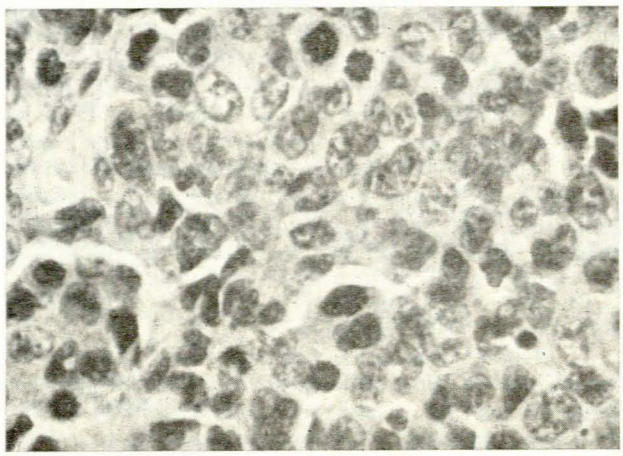

Fig. 5. Large cleaved cell — the classification of Lukes and Collins is the only one to recognize this cell as forming a distinct type. This large cell has an irregular cleaved nucleus and fairly prominent cytoplasm. (H and E × 400.)

The histiocytic group is mentioned by all except the WHO classification. Morphologically it resembles the immunoblast but has abundant acidophilic amorphous cytoplasm, a smaller nucleus and less marked nucleoli (Fig. 6). The nuclear chromatin tends to be more clumped than in the immunoblast.[39] Lukes and Collins[33] maintain that it cannot always be differentiated morphologically from an immunoblast. On lymph node imprints it is positive on alpha-naphthyl-acetate esterase staining.[33]

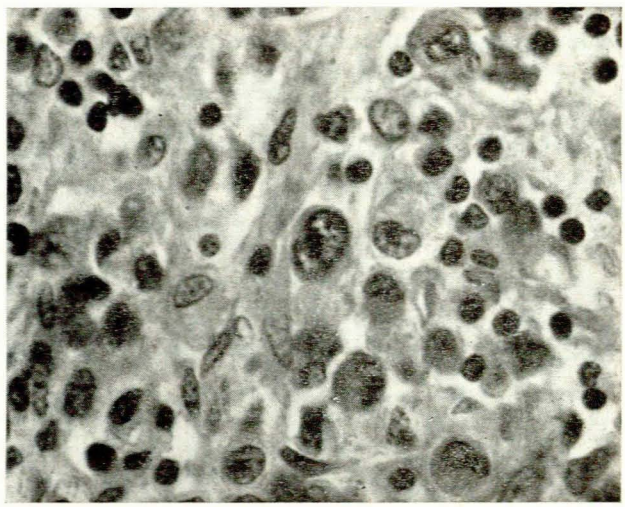

Fig. 6. Histiocytes — these cells differ in appearance from the immunoblasts. They have abundant acidophilic cytoplasm, a smaller nucleus and less prominent nucleoli. Their nuclei are sometimes indented and also vary in size. On lymph node imprints they are positive with alpha-naphthyl-acetate esterase stains. (H and E × 500.)

Until recently, patients with advanced diffuse histiocytic lymphoma or reticulum cell sarcoma have been regarded as having a uniformly fatal disease. In the last decade, the complete remission rate in the treatment of advanced diffuse histiocytic lymphoma has risen from 10% to 78% with the use of combination chemotherapy.[48] Subdivision of the large-cell lymphomas is not as yet of prognostic significance, and it remains to be seen whether classification based on histology, cytology, histochemistry and cytochemistry will be of clinical use.

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